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(71) Applicant (for all designated States except US): SUN PHARMACEUTICAL INDUSTRIES LIMITED [IN/IN]; Acme Plaza, Andheri Kurla Road, Andheri (East), Mumbai 400 059 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): THENNATI, Rajamannar [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN). REHANI, Rajeev, Budhdev [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN). SONI, Rohit, Ravikant [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN). CHHABADA, Vijay, Chhangamal [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN). PATEL, Vijaykumar, Mutlibhai [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN).

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A2

(54) Title: OPTICALLY ACTIVE SUBSTITUTED PYRIDINYL METHYL-SULPHINYL-BENZIMIDAZOLE AND SALTS

WO 03/089408

(57) Abstract: The present invention relates to an enantioselective catalytic oxidation process for preparation of an optically active enantiomer or an enantiomerically enriched form of substituted pyridinylmethyl-sulphinyl-benzimidazole comprising enantioselective catalytic oxidation of a substituted pyridinylmethyl prochiral sulphide derivative of benzimidazole with an oxidizing agent in an organic solvent in the presence of a base and a catalyst comprising titanium or vanadium complexed with a chiral monodentate ligand. The present invention also relates to alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1H-benzimidazole substantially free of sulfone impurity. The present invention also relates to a process for purification of alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1H-benzimidazole comprising treatment of the said alkali or alkaline earth metal salt having a sulfone impurity with a solvent system comprising an organic solvent selected from ketone and nitrile, and isolating the alkali or alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1H-benzimidazole which is substantially free of sulfone impurity.



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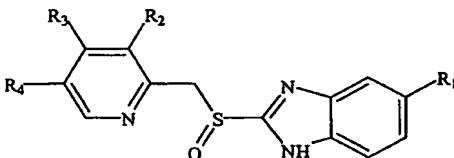
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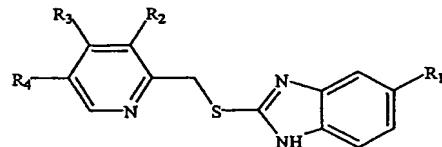
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**OPTICALLY ACTIVE SUBSTITUTED PYRIDINYL METHYL-SULPHINYL-
BENZIMIDAZOLE AND SALTS**

The present invention relates to a process for the preparation of an optically active enantiomer or an enantiomerically enriched form of substituted pyridinylmethyl-sulphinyl-benzimidazole, compound of **formula 1** wherein R₁ to R₄ may be selected from H, linear or branched (1-4C) alkyl, linear or branched (1-4 C) alkoxy, aryl, aryloxy and their halo or alkoxy substituted analogs, by enantioselective catalytic oxidation of a substituted pyridinylmethyl prochiral sulphide derivative of benzimidazole, compound of **formula 2**.



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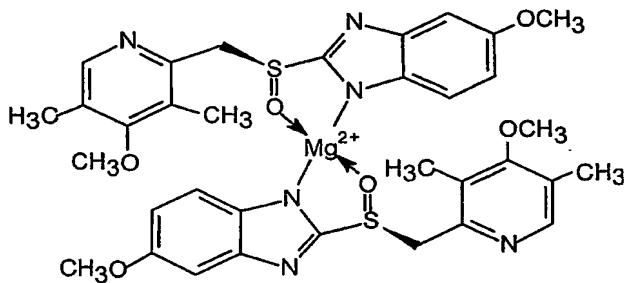
Formula 1**Formula 2**

Optically active substituted pyridinylmethyl-sulphinyl-benzimidazole enantiomers and their pharmaceutically acceptable salts are proton pump inhibitors, which are useful in the treatment of ulcers.

15

More specifically the present invention relates to a process for the preparation of the magnesium salt of 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinyl methyl) sulphinyl]-1*H*-benzimidazole [esomeprazole or S-omeprazole], a compound of **Formula 3**.

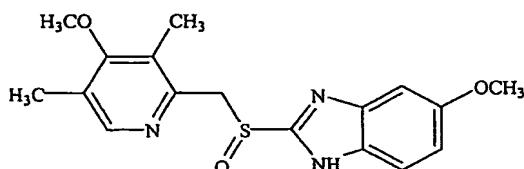
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Formula 3

The present invention also relates to the alkali and alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, a compound of **formula 4**, substantially free of sulfone impurity and a process for preparation thereof. S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]- 1*H*-benzimidazole which is known as esomeprazole and its pharmaceutically acceptable salts are used as antiulcerative agents.



Formula 4

10 **PRIOR ART:**

PCT publication WO 9427988 discloses optically pure compounds characterized in that the compounds are Na⁺, Mg²⁺, Li⁺, K⁺, Ca²⁺ and N⁺(R)₄ salts of (+) and (-) 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1*H*-benzimidazole, wherein R is an alkyl with 1-4 carbon atoms. This invention also claims the process for the preparation of these compounds characterized in that a diastereomeric ester with a chiral acyl group such as mandeloyl, having either R or S configuration, is separated and each of the separated diasteromers is dissolved in an alkaline solution where the acyloxymethyl group is hydrolyzed to give the optically pure compound. This is a laborious process as it involves oxidation, resolution, separation and hydrolysis of the ester to yield the optically active omeprazole and there is large wastage of the unwanted isomer. It does not yield the optically active omeprazole directly on oxidation.

United States Patent No. 5948789 provides a process for enantioselective synthesis of a sulphoxide compound or an alkaline salt thereof in the form of a single enantiomer or in an enantiomerically enriched form comprising oxidizing a prochiral sulfide with an oxidizing agent and in presence of a chiral titanium complex and a base, and optionally converting the obtained sulfoxide into a pharmaceutically acceptable salt by a

conventional process. The examples in the patent use only the chiral bidentate ligand of diethyl tartrate and the use of a catalyst with a chiral monodentate ligand is not disclosed. The exemplified preparation of esoemprazole in this patent provides esomeprazole with sulfone impurity of 2.7% in example 5 and with sulfone impurity of 3.8% in Example 9.

5

PCT publication WO 9617076 claims the stereoselective bio-oxidation of the prochiral sulfide to the corresponding single enantiomer or in an enantiomeric enriched form of sulphinyl derivative. This invention does not disclose chemical oxidation using oxidizing agents such as cumene hydroperoxide.

10

PCT publication WO 9617077 claims the enantioselective preparation of pharmaceutically active sulphoxides by bioreduction. This invention does not disclose chemical oxidation using oxidizing agents such as cumene hydroperoxide.

15

PCT publication WO 9702261 claims a process for the optical purification of enantiomerically enriched preparation of esomeprazole and other similar compounds by treating with a solvent, precipitating the racemate, filtering off the racemate and solvent evaporation to yield the single enantiomer. This invention does not disclose catalytic oxidation of prochiral sulphides to the corresponding sulphinyl derivatives.

20

PCT publication WO 9828294 claims the S-omeprazole in a neutral form in a solid state. This invention does not disclose the catalytic oxidation of prochiral sulphides to the corresponding sulphinyl derivatives in the presence of a catalyst with a chiral monodentate ligand.

25

PCT publication WO 9854171 claims the process of preparing the magnesium salt of S-omeprazole by treating the potassium salt of S-omeprazole with a magnesium source in water. This invention does not disclose catalytic oxidation of prochiral sulphides to the corresponding sulphinyl derivatives in the presence of a catalyst with a chiral monodentate ligand.

PCT publication WO 0044744 claims the potassium salt of S-omeprazole form B hydrate. It does not disclose catalytic oxidation of prochiral sulphides to the sulphanyl derivatives thereof, in the presence of a catalyst with a chiral monodentate ligand.

5 German Patent No. 4035455 claims enantiomerically pure (pyridylmethylsulphanyl)benzimidazoles by derivatizing their racemates (or racemate salts) at the benzimidazole N with an enantiomerically pure chiral compound, separating the resulting diastereomeric derivatives, and solvolyzing the separated derivative isomers in a strongly acidic medium. This invention does not disclose catalytic oxidation of
10 prochiral sulphides to the corresponding sulphanyl derivatives.

The PCT application WO 03/008406 relates to an improved process for the preparation of benzimidazole-type proton pump inhibitors prepared by oxidation of corresponding sulphide wherein the sulfone impurity is removed by extraction with an aqueous alkaline
15 solution at controlled pH. This process was applied on racemic benzimidazoles and not to S-omeprazole. When applied to the racemic compounds the % of sulfone was more than 0.2% in the final pure product.

Pharmaceutically active moieties possessing chirality need to be resolved to check the
20 potency and untoward side-effects of the antipodes. Standard method of separating the unwanted isomer from a racemic mixture is by resolution using resolving agents and solvents. Resolution techniques can be employed for compounds possessing acidic, basic or hydroxyl groups by salt formation or derivatisation with appropriate chiral reagents.

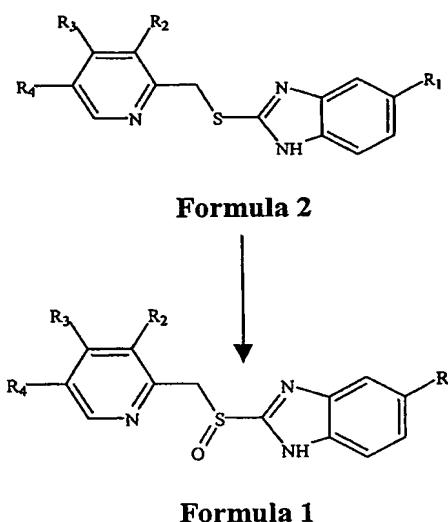
25 However chiral compounds like sulfoxides, hydrocarbons, nitro compounds, nitriles and several other neutral molecules do not possess the necessary features essential for resolution by a classical resolution technique. Thus these compounds have to be synthesised as pure isomers during the bond formation process itself, using chiral reagent as an auxiliary or a catalyst. Moreover methods to resolve optically pure sulfoxides are
30 limited due to neutral nature of the sulfoxide functionality, thus it is difficult to make derivative and resolve the racemic sulfoxides. Also many of the Sulfoxides are liquids

hence enrichment of the enantiomeric purity by way of crystallization is also of limited use.

Methods that are currently adopted to make chiral sulphoxides involve the usage of 5 bidentate chiral ligands such as Sharpless's $Ti(O^iPr)_4$ / Diethyltartrate catalyst conditions or Uemura's $Ti(O^iPr)_4$ / Binol catalyst process. Although these oxidant systems offer many advantages, however in cases where the enantioselectivity is low, the above mentioned oxidant systems offer no options to improve the selectivity, since there is not much scope to make diverse Tartrates or Binols as asymmetric reagents. Hence there is a 10 need to develop a system wherein one can choose an appropriate chiral reagent from a pool of reagents to optimise the chiral purity or enantiomeric excess.

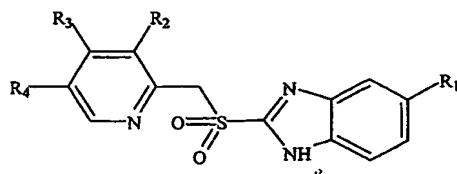
Typically, benzimidazole-type compounds of formula 1 are prepared by oxidation of the sulphide intermediates of formula 2.

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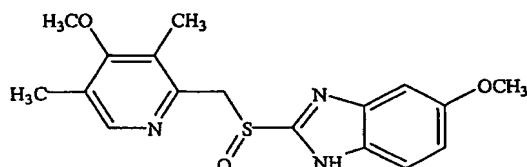
The main problem with the oxidation reaction to convert the sulfide intermediate of formula 2 into the sulfoxide compounds of formula 1 is over-oxidation, i.e. oxidation from sulfoxides of formula 1 to sulfones of **formula 5**. The removal of sulfone impurities has often proved to be difficult, time-consuming and costly.

**Formula 5**

The present invention achieves this object by providing a simple process for removal of sulfone impurity to provide benzimidazole-type compounds of formula 1 substantially free of the sulfone impurity, a compound of formula 5.

The process of enantioselective oxidation, on increasing reaction scale, invariably leads to the formation of variable quantity (1 to 10%w/w) of an impurity, the sulfone derivative, an over oxidized product of 5-methoxy-2-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)thio-1*H*-benzimidazole. Formation of sulfone impurity in excess of 1% w/w, during the course of reaction, renders it difficult to purify and obtain high quality and quantity of the S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl) sulfinyl]-1*H*-benzimidazole and its pharmaceutically acceptable salts.

15 In particular, the present invention provides alkali and alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, a compound of **formula 4**, substantially free of sulfone impurity and a process for preparation thereof.



20

Formula 4

OBJECT OF THE INVENTION

The object of the present invention is to provide a convenient enantioselective catalytic oxidation process for the preparation of an optically active enantiomer or an

enantiomerically enriched form of substituted pyridinylmethyl-sulphinyl-benzimidazole, compounds of **formula 1**.

Another object of the present invention is to provide an alkali or alkaline earth metal salts 5 of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, a compound of formula 4, substantially free of sulfone impurity.

One more object of the present invention is to provide a simple and easy process for preparation of an alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-10 methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, a compound of formula 4, substantially free of sulfone impurity.

More particularly the object of the present invention is to provide a facile and an inexpensive process for the preparation of an optically active substituted pyridinylmethyl-15 sulphinyl-benzimidazole enantiomer, compound of **formula 1**, by enantioselective catalytic oxidation of a substituted pyridinylmethyl prochiral sulphide derivative of benzimidazole, compound of **formula 2**, with an oxidizing agent in an organic solvent in the presence of a base and a catalyst complexed with a chiral monodentate ligand such that the suitable catalyst chiral monodentate ligand complex helps in providing an 20 enantiomeric excess of the desired optically active enantiomer.

The method of enantioselective catalytic oxidation disclosed in the process of the present invention provides diverse pool of reagents to achieve the optical purity and provides enantiomeric excess greater than 98%. Use of tertiary amine bases like 25 diisopropylethylamine enhances chiral induction leading to the formation of chiral sulphoxides.

It is a more specific object to provide a facile and inexpensive process for the preparation of an optically active S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-30 pyridinylmethyl)sulphinyl]-1*H*-benzimidazole (esomeprazole) by enantioselective catalytic oxidation of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-

1*H*-benzimidazole with an oxidizing agent in an organic solvent in the presence of a base and a catalyst complexed with a chiral monodentate ligand such that the selected catalyst chiral monodentate ligand complex provides an enantiomeric excess of the desired optically active enantiomer, esomeprazole.

5

Yet another object of the process of the present invention is to provide a method to prepare the alkali and/or alkaline earth metal salts of optically active substituted pyridinylmethyl-sulphinyl- benzimidazole enantiomers without the need of separating the unwanted isomer, by employing resolution technique's which could be tedious, and 10 uneconomical.

It is yet another more specific object of the present invention to provide a method to prepare the magnesium salt 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulphinyl]-1*H*-benzimidazole by an enantioselective catalytic oxidation 15 process without the need of separating the unwanted R isomer. Resolution and separation of the unwanted isomer would be an economically non-viable and time-consuming alternative.

One more object of the present invention is to provide an alkali or alkaline earth metal 20 salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, a compound of formula 4, substantially free of sulfone impurity.

Another object of the present invention is to provide a process for preparation of alkali or 25 alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, a compound of formula 4, substantially free of sulfone impurity.

The present invention provides salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone 30 impurity, wherein the salts are selected from alkaline earth metal and alkali metal salts.

More specifically the alkali metal salts may be sodium, potassium or lithium; and the alkaline earth metal salts may be magnesium, calcium or barium.

5 The pharmaceutically acceptable salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole of the present invention are substantially free of sulfone impurity which does not exceed 0.5% w/w of the salt.

In most preferred embodiments the sulfone impurity does not exceed 0.2% w/w of the salt.

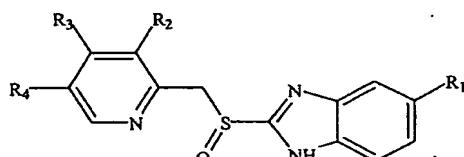
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In another preferred embodiments the sulfone impurity is absent or not detected by analytical methods such as HPLC.

SUMMARY OF INVENTION:

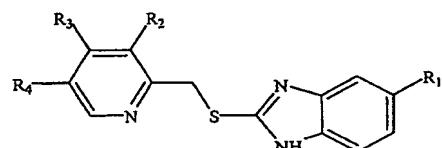
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The present invention provides a process for the preparation of an optically active enantiomer or an enantiomerically enriched form of substituted pyridinylmethylsulphinyl-benzimidazole, compound of **formula 1** wherein R₁ to R₄ are selected from H, linear or branched (1-4C) alkyl, linear or branched (1-4 C) alkoxy, aryl, aryloxy and their 20 halo or alkoxy substituted analogs, said process comprising enantioselective catalytic oxidation of a substituted pyridinylmethyl prochiral sulphide derivative of benzimidazole, compound of **formula 2** wherein R₁ to R₄ are as defined above, with an oxidizing agent in an organic solvent in the presence of a base and a catalyst comprising titanium or vanadium complexed with a chiral monodentate ligand.



25

Formula 1



Formula 2

The present invention also provides alkali and alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, substantially free of sulfone impurity.

5 The present invention also provides a process for purification of alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole comprising treatment of the said alkali or alkaline earth metal salt having a sulfone impurity with a solvent system comprising an organic solvent selected from ketone and nitrile, and isolating the alkali or alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole which is substantially free of sulfone impurity.

10 15 The solvent system used for purification of alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole further comprises an aqueous salt solution of a neutral salt of alkali or alkaline earth metal.

20 **DETAILED DESCRIPTION OF THE INVENTION:**

Compounds prepared by the enantioselective catalytic oxidation process of the present invention are optically active enantiomer or enantiomerically enriched forms of substituted pyridinylmethyl-sulphinyl-benzimidazole, compound of **formula 1**.

25 More specifically the process of the present invention provides an enantioselective catalytic oxidation process for the preparation of optically active or enantiomerically enriched sulfoxides of omeprazole, pantoprazole, rabeprazole and lansoprazole which are proton pump inhibitors useful in the treatment of ulcers.

30

The process of the present invention further provides a process for the preparation of alkali and/or alkaline earth metal salt of an optically active enantiomer or an enantiomerically enriched form of substituted pyridinylmethyl-sulphinyl-benzimidazole, compound of **formula 1**, prepared by enantioselective catalytic oxidation of a substituted 5 pyridinylmethyl prochiral sulphide derivative of benzimidazole, compound of **formula 2**.

The process of the present invention comprises enantioselective catalytic oxidation of prochiral sulphides with an oxidizing agent in an organic solvent in the presence of a base 10 and a catalyst comprising titanium or vanadium complexed with a chiral monodentate ligand.

According to the preferred embodiment of the process of the present invention the oxidizing agent may be selected from hydrogen peroxide, alkyl hydroperoxides and 15 arylalkyl hydroperoxide, preferably alkyl hydroperoxides and/or arylalkyl hydroperoxide. More preferably, the oxidising agent is an arylalkyl hydroperoxide, the most preferred being cumene hydroperoxide. The mole ratio of the oxidizing agent to the prochiral sulphide that may be used is between the range from 0.8:1 to 1.5:1, more preferably between the range from 1:1 to 1.2:1.

20

The catalyst comprising titanium or vanadium complexed with a chiral monodentate ligand that can be used may be prepared by reacting a titanium or vanadium reagent with a chiral monodentate ligand. The titanium or vanadium reagent may be selected from titanium alkoxides or vanadium acetate. Preferably the reagent is a titanium reagent 25 selected from alkoxides of Ti(IV), more preferably isopropoxide of Ti(IV). The mole ratio of the titanium or vanadium reagent to the prochiral sulphide that may be used range from 0.05:1 to 0.5:1, the most preferred being 0.25:1 to 0.35:1.

The chiral monodentate ligand may be selected from a pool of chiral alcohol moieties like 30 diaryl alcohol, dialkyl alcohols, alkyl aryl alcohols, alkyl or aralkyl α -hydroxy acids (alkyl residues may be linear, branched, cyclic, etc with 1C to 20C carbon chain) or aryl,

substituted aryl or heteroaryl α -hydroxy acetic acids and their derivatives such as esters, amides, hydrazides, hydroxamic acids *etc.* The more preferred being the aryl or substituted aryl α -hydroxy acetic acid esters, preferably lower alkyl esters of R or S mandelic acid, the most preferred being R(-) or S(+) Methyl mandelate, as the case may 5 be. The mole ratio of the chiral monodentate ligand to the prochiral sulphide that may be used range from 1.2:1 to 3:1, most preferably 2:1 to 2.5:1.

According to the process of the present invention the enantioselective catalytic oxidation process is carried out in the presence of a base. The base may be an organic amine base 10 selected from a group of primary, secondary or tertiary amines, preferably the hindered, alkyl, cyclic alkyl, aralkyl primary, secondary or tertiary amines, more preferably the hindered alkyl tertiary amines, the most preferred being N,N-diisopropylethylamine. The mole ratio of the base to the prochiral sulphide that may be used range from 0.05:1 to 1:1, most preferably 0.05:1 to 0.2:1.

15 In the enantioselective catalytic oxidation process of the present invention the organic solvent that may be used is selected from halo substituted or unsubstituted alkyl and aryl hydrocarbons such as hexane, toluene, xylenes, methylene chloride, chlorobenzene and the like, alkyl or aryl ketones like acetone, methylisobutyl ketone, methylethyl ketone 20 and the like, alky or aryl nitriles like benzonitrile, acetonitrile and the like. The preferred solvents include toluene, acetonitrile and methylisobutylketone.

According to the enantioselective catalytic oxidation process of the present invention the preparation of the catalyst is carried out in the presence of the prochiral sulphide or 25 before the addition of the prochiral sulphide, preferably before the addition of the prochiral sulphide.

The temperature during the preparation of the catalyst, by treating titanium or vanadium reagent with a chiral monodentate ligand, may be about 30-70 $^{\circ}$ C, most preferably about 30 40-50 $^{\circ}$ C. The time for preparation of the catalyst may range from about 1-24 hours, the most preferred being about 17-22 hours.

According to the process of the present invention the enantioselective catalytic oxidation reaction may be carried out at a temperature between the range of about 20-40 °C, more preferably between the range of about 25-30°C for a period of 1-8 hrs, most preferably 5 for about 2-6 hrs.

The optically active substituted pyridinylmethyl-sulphinyl- benzimidazole compound of formula 1 is separated by treating the oxidized reaction mixture with an aqueous basic solution like aqueous ammonia solution followed by extraction with the same or different 10 solvent.

The process of the present invention further comprises preparing an optically active alkali and/or alkaline earth metal salt of substituted pyridinylmethyl-sulphinyl-benzimidazole by treating the optically active substituted pyridinylmethyl-sulphinyl-benzimidazole 15 compound of formula 1, obtained by enantioselective catalytic oxidation of substituted pyridinylmethyl prochiral sulphide derivative of benzimidazole, compound of **formula 2**, with an alkali and/or alkaline earth metal source. The alkali or alkaline earth metal source may be selected from Na^+ , K^+ , Li^+ , Mg^{+2} , Ca^{2+} salts like bicarbonates, carbonates, hydrides, hydroxides and oxides. Preferably sodium hydroxide, potassium hydroxide, 20 lithium hydroxide and magnesium hydroxide, the most preferred being sodium hydroxide.

The process of the present invention further comprises the steps of isolation of the alkali or alkaline earth metal salts of the optically active substituted pyridinylmethyl-sulphinyl- 25 benzimidazole, compound of **formula 1**, by solvent evaporation with or without vacuum, addition of the same or different solvent and filtering the product, drying followed by crystallization, if required.

According to yet another embodiment, the process of the present invention may further 30 comprise the preparation of the alkaline earth metal salts of the optically active substituted pyridinylmethyl-sulphinyl- benzimidazole, compound of formula 1 by

treating the alkali metal salt of optically active substituted pyridinylmethyl-sulphinyl-benzimidazole, compound of formula 1 with an alkaline earth metal source, preferably an alkaline earth metal halide selected from calcium, magnesium and barium halide, the most preferred being magnesium chloride. The alkaline earth metal salt of optically 5 active substituted pyridinylmethyl-sulphinyl-benzimidazole, compound of formula 1, may be isolated by filtration, drying followed by crystallization, if required.

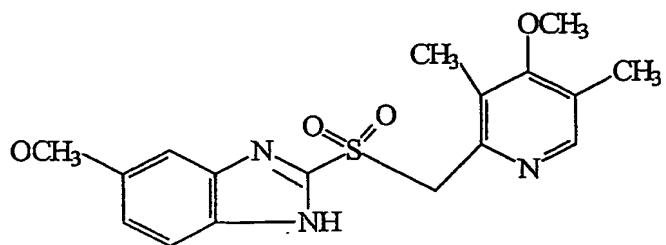
The present invention also provides alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, a 10 compound of formula 4, substantially free of sulfone impurity.

Preferably the present invention provides the alkali and alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole wherein the sulfone impurity is less than 0.5 %w/w.

15 More preferably the present invention provides the alkali and alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole wherein the sulfone impurity is less than 0.2 %w/w.

20 The present invention also provides a process for purification of alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole comprising treatment of the said alkali or alkaline earth metal salt having a sulfone impurity with a solvent system comprising an organic solvent selected from ketone and nitrile, and isolating the alkali or alkaline earth 25 metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole which is substantially free of sulfone impurity.

30 The salt of the S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole contain sulfone impurity, a compound of formula 6, which can be removed by purification process of the present invention.



Formula 6

According to the purification process of the present invention the sulfone impurity is removed from salt of the S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1H-benzimidazole by treatment with a solvent system comprising an organic solvent selected from ketone and nitrile. Preferably the solvent could be a ketone or a nitrile having C₂ to C₁₀ carbon chain, which could be linear, branched or cyclic. The preferred solvents are acetone, acetonitrile, methylisobutyl ketone, methylethyl ketone and the like. The most preferred solvent is acetone.

10

The solvent system of the purification process of the present invention can further comprise an aqueous salt solution of a neutral salt of alkali or alkaline earth metal.

Any neutral salt of alkali or alkaline earth metal may be used in the solvent system used for removal of sulfone impurity. Examples of neutral salt of alkali or alkaline earth metal include sodium chloride (NaCl), potassium chloride (KCl), barium chloride, calcium chloride and the like. The preferred neutral salt is NaCl.

The solvent system used for removal of sulfone impurity in the process of the present invention may comprise the organic solvent and an aqueous salt solution of a neutral salt of alkali or alkaline earth metal in the ratio of between the range from 99.9:0.1 to 99.3:0.7 v/v.

In the solvent system of the present invention, the concentration of the aqueous solution of the neutral salt of alkali or alkaline earth metal is in the range between 0.5 to 5 %w/v., preferably in the range between 0.5 to 1 %w/v. The preferred neutral salt is NaCl.

In a preferred embodiment the solvent system used for purification process comprises acetone.

5 In another preferred embodiment the solvent system used for purification process comprises acetone and aqueous solution of NaCl.

The ratio of organic solvent and aqueous salt solution of neutral alkali or alkaline earth metal salt may be selected so as to maximise the sulfone impurity in soluble state. This 10 specific combination helps in ensuring elimination of the sulfone impurity to the desired level and providing the pure S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole salt as an insoluble filterable mass. The optimum ratio may be appropriately selected by one skilled in the art based on the sulfone content present in the product. The sulfone content of up to 4% can be 15 effectively removed by the process of the present invention.

In yet another preferred embodiment the solvent system comprises acetone:aqueous salt solution of NaCl in the ratio of between the range from 99.9:0.1 to 99.3:0.7, preferably 20 99.3:0.7.

According to the purification process of the present invention the treatment with the solvent system may be carried out for example, by refluxing with the solvent system for a period of about 1 to about 8 hours, preferably about 1 to about 2 hours.

25 The reaction may be monitored for the levels of sulfone impurity by standard analytical techniques like TLC, HPLC. Alkali metal or alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity is then isolated by conventional means such as 30 filtration and drying.

The alkali metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity obtained by following the process of the present invention can be converted to alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity by reacting with an alkaline earth metal source. The alkaline earth metal source that may be used may be calcium, magnesium or barium salts like chlorides. For example, magnesium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity may be prepared from sodium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity prepared by following the process of the present invention.

In a preferred embodiment the alkali or alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole is prepared according to the enantioselective catalytic oxidation process of the present invention and then purified by purification process of the present invention by treatment with the solvent system.

20 The present invention provides alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity.

In a preferred embodiment the present invention provides alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, wherein the sulfone impurity is less than 0.5%w/w.

In a more preferred embodiment the present invention provides alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-

pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, wherein the sulfone impurity is less than 0.2%w/w.

5 In yet another preferred embodiment the present invention provides alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole, wherein the sulfone impurity is absent or not detected by analytical methods such as High Performance Liquid Chromatograph (HPLC).

10 In a preferred embodiment the present invention provides sodium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity.

15 In another preferred embodiment the present invention provides sodium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole wherein the sulfone impurity is less than 0.5%w/w.

20 In yet another preferred embodiment the present invention provides sodium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole wherein the sulfone impurity is less than 0.2%w/w.

25 In a preferred embodiment the present invention provides magnesium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity.

In another preferred embodiment the present invention provides magnesium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole wherein the sulfone impurity is less than 0.5%w/w.

In yet another preferred embodiment the present invention provides magnesium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole wherein the sulfone impurity is less than 0.2%w/w.

- 5 In preferred process of the present invention the sulfone impurity in the alkali or alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole obtained does not exceed 0.2%, thus rendering it pharmaceutically acceptable as per ICH guidelines.
- 10 The invention is illustrated but not restricted by the description in the following examples.

EXAMPLES

Example 1: Preparation of a salt of esomeprazole by following enantioselective catalytic oxidation process of the present invention involving Titanium catalyst complexed with a monodentate ligand-

(a) Preparation of sodium salt of 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulphonyl]-1H-benzimidazole (esomprazole sodium)

10 Mix, S-(+)-Methyl mandelate 60.6 g, Toluene 250 ml and Titanium isopropoxide 15 ml, into a 500 ml R.B.Flask assembly and stir to make a clear solution under Nitrogen atmosphere. Heat the reaction mixture to 40°C and maintain for 17 hr. Cool to 25-30°C and charge Omeprazole sulfide 50 g and Diisopropylethylamine 1.35 ml to it and stir for 10-15 minutes. Add Cumene hydroperoxide (~ 80 % solution in cumene) 28 ml

15 slowly through addition funnel to the reaction mixture at 25-30°C. Stir the reaction mixture at 25-30°C for 2.0 hr. Filter the solid and wash with Toluene 50 ml. Collect the filtrate and charge 12.5 % ammonia solution 300 ml, to the filtrate and stir the mixture for 15 minutes. Back extract the Toluene layer with 12.5% Ammonia solution ; 200 ml and add Methyl isobutyl ketone 250 ml, to the combined aqueous layer. Adjust the pH of

20 the solution to 7.3-7.6 by adding Glacial Acetic acid at 25- 30 °C. Stir the content for 30 min. Separate the organic layer and extract the aq. layer with Methyl isobutyl ketone ; 50 ml. Charge sodium hydroxide solution (50% w/v) 11 ml to combined organic layer and stir the mixture for 15 minutes. Distil off solvent completely under vacuum at 55-60 °C. Add Acetonitrile; 300 ml, to the residue and stir the content at 25-30°C. Filter the product

25 under nitrogen atmosphere and wash the cake with Acetonitrile 50 ml. Dry the product in vacuum at 50-55°C. Yield of Esomeprazole sodium (22.4 g) with enantiomeric excess > 98%.

30 **(b) Preparation of 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulphonyl]-1H-benzimidazole magnesium (esomprazole magnesium)**

Mix, esomeprazole sodium prepared in Example 1, 20 g and Distilled water, 200 ml, into a 500 ml R.B.flask Add a solution Magnesium chloride, 11 g in Distilled water, 50 ml,

slowly through addition funnel in 30 minutes at 25-30°C. Stir the reaction mixture for 1.0 hr. Filter the product and wash the cake with Distilled Water, 60 ml. Dry the product in vacuum at 50-55°C. Yield of Esomeprazole magnesium = 15 g with an enantiomeric excess >98%.

5

Example 2 -Preparation of a salt of esomeprazole by following a known process involving Titanium catalyst complexed with a bidentate ligand

Preparation of sodium salt of 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulphonyl]-1H-benzimidazole (esomprazole sodium) -

10

Mix, Toluene 120 L, Omeprazole sulfide 30 Kg, followed by 204 ml Water, D-(-)-Diethyl tartrate 9.4 L and Titanium isopropoxide 7.98 Kg, into a 500 L reaction assembly and stir to make a homogenous suspension under Nitrogen atmosphere. Heat the reaction mixture to 50-52°C and maintain for 1 hour. Cool to 15-20°C and charge 15 Diisopropylethylamine 3.56 Kg to it and stir for 10-15 minutes. Add Cumene hydroperoxide (~ 80 % solution in cumene) 16.37 Kg slowly through addition funnel to the reaction mixture at 0 to 5°C.

Stir the reaction mixture at 25-30°C for 2.0 hr. Charge 12.5 % ammonia solution 240 L, 20 to it and stir for 10-15 minutes. Back extract the Toluene layer with 12.5% Ammonia solution ; 60 L and add Methyl isobutyl ketone 120 L, to the combined aqueous layer. Adjust the pH of the solution to 7.3-7.6 by adding Glacial Acetic acid at 25- 30 °C. Stir the content for 30 min. Separate the organic layer and extract the aq. layer with Methyl isobutyl ketone ; 30 L. Charge sodium methoxide solution (30% w/v) about 15 Kg to 25 combined organic layer and stir the mixture for 15 minutes. Distil off solvent completely under vacuum at 55-60 °C. Add Acetonitrile; 90 L to the residue and stir the content at 25-30°C. Filter the product under nitrogen atmosphere and wash the cake with Acetonitrile 60 L. Dry the product in vacuum at 50-55°C.
Yield of Esomeprazole sodium = about 18 Kg.

30 Sulfone content : 4.0 %

Example 3- Purification of esomeprazole salt by purification process of the present invention

Suspend 100g of esomeprazole sodium (moisture content about 1% & sulfone content about 0.8 %) in a 1 L Acetone. Heat the above contents for a period of 1 hour at reflux

5 temperature, then cool it to 35-38 °C and filter the product at 35-38 °C.

The % of sulfone in the product is less than 0.2 %.

The yield of isolated product is 85 g.

Example 4- Purification of esomeprazole salt by purification process of the present invention

10 Suspend 100g of esomeprazole sodium (moisture content about 1% & sulfone content about 4 %) in a mix of 1 L Acetone and aqueous NaCl (the ratio of Acetone: aqueous

NaCl is 99.3 : 0.7 and the concentration of NaCl in water is about 5 %). Heat the above

contents for a period of 1 hour at reflux temperature, then cool it to 35-38°C and filter the

15 product at 35-38 °C.

The % of sulfone in the product is less than 0.2%.

The yield of isolated product is 65 g.

Example 5-

20 Preparation of 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulphinyl]-1H-benzimidazole magnesium (esomprazole magnesium)

Mix 30 g of esomeprazole sodium prepared in Example 3, and 300 ml of distilled water, into a 500 ml R.B.flask Add a solution Magnesium chloride, 16.7 g in Distilled water,

25 60 ml, slowly through addition funnel in 30 minutes at 25-30°C. Stir the reaction mixture for 1.0 hr. Filter the product and wash the cake with Distilled Water, 60 ml. Dry the product in vacuum at 50-55°C.

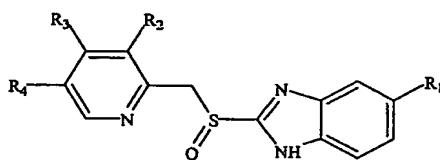
Yield of Esomeprazole magnesium = 26 g with an enantiomeric excess >98%.

HPLC purity: 99.76 % and Sulfone content: 0.07 %

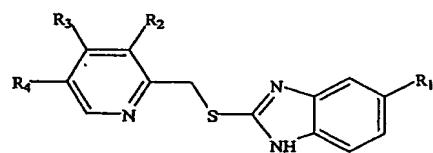
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We claim:

1. An enantioselective catalytic oxidation process for the preparation of an optically active enantiomer or an enantiomerically enriched form of substituted pyridinylmethyl-sulphinyl-benzimidazole, compound of **formula 1** wherein R₁ to R₄ are selected from H, linear or branched (1-4C) alkyl, linear or branched (1-4 C) alkoxy, aryl, aryloxy and their halo or alkoxy substituted analogs, said process comprising enantioselective catalytic oxidation of a substituted pyridinylmethyl prochiral sulphide derivative of benzimidazole, compound of **formula 2** wherein R₁ to R₄ are as defined above, with an oxidizing agent in an organic solvent in the presence of a base and a catalyst comprising titanium or vanadium complexed with a chiral monodentate ligand.



Formula 1



Formula 2

15 2. A process as claimed in claim 1 further comprising preparing an optically active alkali or alkaline earth metal salts of the compound of **formula 1** by treating the compound of **formula 1** with an alkali or alkaline earth metal source.

20 3. A process as claimed in claim 2 further comprising treating the optically active alkali metal salt of the compound of **formula 1** with an alkaline earth metal source to yield the alkaline earth metal salt of the optically active compound of **formula 1**.

4. A process as claimed in claim 1 wherein the oxidising agent is selected from hydrogen peroxide, alkyl hydroperoxides and alkylaryl hydroperoxide.
5. A process as claimed in claim 4 wherein the oxidising agent is cumene hydroperoxide.
6. A process as claimed in claim 4 wherein the mole ratio of the oxidising agent to the prochiral sulphide is between the range from 0.8:1 to 1.5:1.
- 10 7. A process as claimed in claim 1 wherein the base is an organic amine base.
8. A process as claimed in claim 7 wherein the organic amine base is N,N-diisopropylethylamine.
- 15 9. A process as claimed in claim 1 wherein the mole ratio of the base to the prochiral sulphide is in the range 0.05:1 to 1:1.
10. A process as claimed in claim 1 wherein the catalyst is prepared by reacting titanium or vanadium reagent with a chiral monodentate ligand.
- 20 11. A process as claimed in claim 10 wherein the titanium reagent is selected from alkoxides of Ti (IV).
- 25 12. A process as claimed in claim 11 wherein the titanium reagent is isopropoxide of Ti (IV).
13. A process as claimed in claim 1 wherein the chiral monodentate ligand is selected from S(+) methyl mandelate or R(-) methyl mandelate.
- 30

14. A process as claimed in claim 10 wherein the catalyst is prepared before the addition of the prochiral sulphide.
- 5 15. A process as claimed in claim 10 wherein the catalyst is prepared at temperature between the range of about 30 to about 70°C.
16. A process as claimed in claim 15 wherein preparation of the catalyst is carried out for a period of about 1 to about 24 hours.
- 10 17. A process as claimed in claim 15 wherein the catalyst is prepared at temperature between the range of about 40 to about 50°C.
18. A process as claimed in claim 17 wherein preparation of the catalyst is carried out for a period of about 17 to about 22 hours.
- 15 19. A process as claimed in claim 11 wherein the mole ratio of Ti (IV) reagent to the prochiral sulphide is 0.05:1 to 0.5:1.
- 20 20. A process as claimed in claim 1 wherein the mole ratio of the chiral monodentate ligand to the prochiral sulphide is 1.2:1 to 3:1.
21. A process as claimed in claim 1 wherein the organic solvent is selected from the group of toluene, methylisobutyl ketone and acetonitrile.
- 25 22. A process as claimed in claim 1 wherein the enantioselective catalytic oxidation is carried out at a temperature between the range of about 20 – 40°C.
23. A process as claimed in claim 1 wherein the enantioselective catalytic oxidation is carried out for a period of about 1 – 8 hours.

30

24. A process as claimed in claim 1 wherein the process further comprises the step of treating the reaction mass after enantiomeric catalytic oxidation with an aqueous ammonia solution.

5 25. A process as claimed in claim 2 wherein the optically active alkali or alkaline earth metal salt is prepared by treating with alkali or alkaline earth metal source selected from either of Na^+ , K^+ , Li^+ , Mg^{+2} , Ca^{2+} salts like bicarbonates, carbonates, hydrides, hydroxides and oxides.

10 26. A process as claimed in claim 3 wherein the optically active alkali metal salt is treated with alkaline earth metal source selected from barium halides, magnesium halides and calcium halides.

15 27. A process as claimed in claim 1 wherein the optically active substituted pyridinylmethyl-sulphanyl-benzimidazole enantiomer is 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulphanyl]-1H-benzimidazole.

20 28. A process for purification of alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1H-benzimidazole comprising treatment of the said alkali or alkaline earth metal salt having a sulfone impurity with a solvent system comprising an organic solvent selected from ketone and nitrile, and isolating the alkali or alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1H-benzimidazole which is substantially free of sulfone impurity.

25 29. The process as claimed in claim 28 wherein said solvent system further comprises an aqueous salt solution of a neutral salt of alkali or alkaline earth metal.

30 30. The process as claimed in claim 28 further comprising reacting the alkali metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-

5
pyridinylmethyl)sulfinyl]-1*H*-benzimidazole with an alkaline earth metal source to yield the alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity.

10

31. The process as claimed in claim 28, 29 or 30 wherein the alkaline earth metal salt is the magnesium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole substantially free of sulfone impurity.

15

32. The process as claimed in claim 28 wherein, the organic solvent is a ketone solvent selected from acetone, methylethyl ketone, methylisobutyl ketone.

33. The process as claimed in claim 32, wherein the ketone solvent is acetone.

20

34. The process as claimed in claim 29, wherein the neutral salt of alkali or alkaline earth metal is selected from NaCl or KCl.

35. The process as claimed in claim 34, wherein the neutral salt is NaCl.

25

36. The process as claimed in claim 28, wherein the solvent system comprises acetone.

30

37. The process as claimed in claim 29, wherein the solvent system comprises acetone and aqueous solution of NaCl.

38. The process as claimed in claim 29, wherein the solvent system comprises the organic solvent and aqueous solution of the said neutral salt of alkali or alkaline earth metal in the ratio between the range from 99.9:0.1 to 99.3:0.7 v/v.

39. The process as claimed in claim 38, wherein the organic solvent is acetone and the neutral salt is NaCl.

40. The process as claimed in claim 39, wherein acetone and aqueous solution of NaCl is in the ratio of 99.3:0.7 v/v.

5

41. The process as claimed in claim 29, wherein the concentration of the said aqueous solution of the neutral salt of alkali or alkaline earth metal is in the range between 0.5 to 5 %w/v.

10

42. The process as claimed in claim 41, wherein the concentration of the said aqueous solution of the neutral salt of alkali or alkaline earth metal is in the range between 0.5 to 1 %w/v.

15

43. The process as claimed in claim 28 wherein treatment with a solvent system is carried out by refluxing in a solvent system wherein the solvent system comprises acetone, and then isolating the alkali or alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole which is substantially free of sulfone impurity.

20

44. The process as claimed in claim 43 wherein the solvent system further comprises aqueous solution of NaCl.

25

45. The process as claimed in claim 44, wherein the solvent system comprises acetone and aqueous solution of NaCl in a ratio between the range from 99.9:0.1 to 99.3:0.7.

46. The process as claimed in claim 45, wherein the solvent system comprises acetone and aqueous solution of NaCl in a ratio of 99.3:0.7 v/v.

30

47. The process as claimed in claim 28 wherein the alkali or alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole is prepared according to the process of claim 2.

5

48. The alkali and alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole wherein the sulfone impurity is less than 0.2%w/w.

10 49. The sodium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole wherein the sulfone impurity is less than 0.2%w/w.

15 50. The magnesium salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole wherein the sulfone impurity is less than 0.2%w/w.

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(71) Applicant (for all designated States except US): SUN PHARMACEUTICAL INDUSTRIES LIMITED [IN/IN]; Acme Plaza, Andheri Kurla Road, Andheri (East), Mumbai 400 059 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): THENNATI, Rajamannar [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN). REHANI, Rajeev, Budhdev [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN). SONI, Rohit, Ravikant [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN). CHHABADA, Vijay, Chhangamal [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN). PATEL, Vijaykumar, Muljibhai [IN/IN]; Sun Pharma Advanced Research Centre, Akota Road, Akota, Baroda 390 020 (IN).

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Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

[Continued on next page]

A3

(54) Title: OPTICALLY ACTIVE SUBSTITUTED PYRIDINYL METHYL-SULPHINYL-BENZIMIDAZOLE AND SALTS

(57) Abstract: The present invention relates to an enantioselective catalytic oxidation process for preparation of an optically active enantiomer or an enantiomerically enriched form of substituted pyridinylmethyl-sulphinyl-benzimidazole comprising enantioselective catalytic oxidation of a substituted pyridinylmethyl prochiral sulphide derivative of benzimidazole with an oxidizing agent in an organic solvent in the presence of a base and a catalyst comprising titanium or vanadium complexed with a chiral monodentate ligand. The present invention also relates to alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1H-benzimidazole substantially free of sulfone impurity. The present invention also relates to a process for purification of alkali or alkaline earth metal salts of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1H-benzimidazole comprising treatment of the said alkali or alkaline earth metal salt having a sulfone impurity with a solvent system comprising an organic solvent selected from ketone and nitrile, and isolating the alkali or alkaline earth metal salt of S-enantiomer of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinylmethyl)sulfinyl]-1H-benzimidazole which is substantially free of sulfone impurity.

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- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00164-0

CLASSIFICATION OF SUBJECT MATTER

IPC⁷: C07D 401/12, B01J 21/06, B01J 31/22, A61K 31/415, A61K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁷: C07D 401/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPOQUE: WPI, EPODOC, PAJ, NPL, MEDLINE, XPESP

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5948789 A (LARSON ET AL) 7 September 1999 (07.09.99) <i>column 4-21.</i>	1-50
X	H. COTTON et al., "Asymmetric synthesis of esomeprazole", Tetrahedron Asymmetry, 11, 2000, pages 3819-3825 <i>the whole document.</i>	1-48,50
X	EP 1277752 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 8 November 2001 (08.11.01) <i>the whole document.</i>	1-47
X	WO 98/54171 A1 (ASTRA AKTIEBOLAK) 3 December 1998 (03.12.98) <i>examples.</i>	48,50

 Further documents are listed in the continuation of Box C. See patent family annex.

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Date of the actual completion of the international search
16 October 2003 (16.10.2003)Date of mailing of the international search report
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Austrian Patent Office
Dresdner Straße 87, A-1200 Vienna
Facsimile No. 1/53424/535Authorized officer
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Telephone No. 1/53424/348

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN 03/00164-0

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